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NUMORPHAN

Oxymorphone (Numorphan - Endo), or 14-hydroxydihydromorphinone, is, as its chemical name indicates, similar to dihydromorphinone USP (Dilaudid - Knoll). Numorphan is promoted as "one of the most significant advances in analgesics since the isolation of morphine in 1805." It is claimed to have "decisive advantages over morphine" in terms of potency, rapidity of onset, duration of action, freedom from side effects, and margin of safety. The introduction of new synthetic narcotics has invariably been accompanied by claims not substantiated by subsequent experience, and Numorphan does not appear to be an exception.

Clinical judgment of relative advantages and disadvantages of analgesics is influenced by many factors, including differences in patients and observers, dosage and mode of drug administration, and - particularly with narcotics - tolerance and cross-tolerance. As The Medical Letter has so often emphasized, unless drugs are evaluated under similar conditions in well-controlled studies, the comparisons are not likely to be reliable. Most of the published reports on clinical investigations of Numorphan do not show that adequate controls were used.

ANALGESIC EFFECTIVENESS - Several well-controlled studies have, however, demonstrated that Numorphan is an effective analgesic. There is good agreement among investigators (S. L. Wallenstein and R. W. Houde, Fed. Proc., 15:495, 1956; N. B. Eddy and L. E. Lee, J. Pharmacol. & Exper. Ther., 125: 116, 1959) that about a tenth as much Numorphan as morphine is required for equal analgesic effect; but in peak effect, rapidity of onset, and duration of analgesic effect, Numorphan and morphine in equi-analgesic doses were found to be almost identical.

The studies do not, therefore, support the claim that Numorphan has a more rapid onset of action and more prolonged duration of effect than morphine. Nor do they support the claims that the drug has a wide margin of safety, and that "in ultrasevere pain, increasing the dose will ensure thorough analgesia." The basis for such claims appears to be the case reports of patients dependent on narcotics who tolerated doses of 5 to 20 mg. without adverse effects (A. Coblentz and H. R. Bierman, N.E. J. Med., 255: 694, 1956). But Eddy and Lee (see above) have reported severe respiratory depression with doses as low as 1.33 mg. The fact that Numorphan is ten times as potent as morphine merely indicates that the

same effect can be produced with one-tenth the dose, and not that Numorphan is capable of relieving more severe pain.

SIDE EFFECTS - The claim that Numorphan produces fewer and less severe side effects than morphine, less respiratory depression, less nausea and vomiting, and less sedative, constipating and cough-inhibiting effects, is by and large based on uncontrolled observations. More experience with the drug is required before such statements can be fully evaluated. One controlled study of the relative respiratory depressant effects of Numorphan and morphine in healthy volunteers (J. W. Bellville, et al., Anesthesiology, 21: 397, 1960) led to the conclusion that Numorphan was at least as depressant as morphine in equi-analgesic doses. Another study on six normal young men and 10 older patients (M. E. Resnick, et al., JAMA, 173: 1649, 1960) confirms this conclusion. Numorphan is a narcotic and subject to federal regulations. It appears to be as addictive as morphine in equivalent analgesic doses.

Numorphan is supplied in ampules and multi-dose vials in concentrations of 1.5 mg. per cc.; it should be kept in mind that this is a dose roughly equivalent to 15 mg. of morphine. In the event of overdosage, nalorphine USP (Nalline - Merck) is an effective antidote. Numorphan is also supplied in 2- and 5-mg. rectal suppositories, but there is very little information on the absorption and effectiveness of the drug by this route.

Numorphan is a useful analgesic-narcotic which - in equivalent doses - is similar to morphine in effectiveness and side effects. Its cost to the physician is, however, many times that of morphine. Numorphan in 10-cc. vials (1.5 mg. per cc.) costs the physician about 35¢ for 1.5 mg. The equivalent dosage of morphine (15 mg.) costs about 4¢ in tablet form and about 8¢ in 20-cc. vials (1/4 gr. per cc.).

DILODERM

Dichlorisone acetate (Diloderm - Schering) is a new topical steroid which appears to have about the same usefulness and limitations in the treatment of skin ailments as other topical steroids. Preliminary clinical tests by Medical Letter consultants indicate that a 0.25% concentration of Diloderm is more or less equivalent in potency to 1% hydrocortisone. Since Diloderm has the disadvantage of being a new and relatively untried agent, however, there is little reason to substitute it for hydrocortisone or other topical steroids.

As the result of a chemical change in the basic steroid molecule (the substitution of chlorine for oxygen at the 11 position of the molecule), dichlorisone has no demonstrable anti-inflammatory action when given systemically even though it retains the local anti-inflammatory effects of the corticosteroids when applied topically.

EFFECTS OF OTHER STEROIDS - If the older topical steroids had systemic effects when applied to the skin, the new product would offer a real advantage. With the single exception of fludrocortisone, however, none of the older topical

steroids are absorbed sufficiently to have any significant systemic effect. Even when steroids are injected directly into patches of dermatoses resistant to topical therapy, the amounts used are so small that systemic effect is negligible.

For a discussion of the use of topical steroids in the treatment of dermatoses, see The Medical Letter, 1:94, Dec. 11, 1959 and 2:12, Feb. 5, 1960. As pointed out in the latter issue, 0.1% triamcinolone acetonide (Kenalog - Squibb; Aristocort Topical - Lederle) has been found in controlled studies to be superior to other topical steroids in the treatment of various dermatoses. Topical steroids are used in many skin conditions in which their effectiveness, if any, is limited to the soothing action of the vehicle. The conditions in which they are likely to be beneficial are atopic dermatitis, lichen simplex chronicus, nummular eczema and, perhaps, seborrheic dermatitis, intertrigo and contact dermatitis.

Diloderm is available in a 0.25% concentration in cream and aerosol forms. A 5-Gm. tube of Diloderm cream costs about $1.25 to $1.50. A 5-Gm. tube of 1% hydrocortisone ointment costs from about $1 to about $2, depending on brand. The cost of Kenalog and Aristocort Topical creams and ointments is about $2 for a 5-Gm. tube.

MEPROBAMATE

One of the drugs evaluated in the first issue of The Medical Letter (Jan. 23, 1959) was meprobamate (Miltown - Wallace; Equanil - Wyeth). The evaluation concluded: "The widely held belief that meprobamate [in the dosages used in office practice] has virtues in relieving anxiety and tension that are unique or different from those of barbiturates does not appear to be justified by available evidence." This conclusion was based largely on a critical survey of the literature on meprobamate by V. G. Lateis and B. Weiss (J. Chronic Dis., 7:500, 1958). Because of the very wide use of this drug, and the rapidly growing number of combinations of meprobamate with other drugs, Medical Letter consultants have reviewed the subsequent literature to see whether any change in the earlier conclusions is warranted.

NEW STUDIES - Although meprobamate in large doses may be useful in the treatment of some psychotic patients, prior to the earlier review not one controlled study had shown smaller doses of the drug to be superior to a placebo in the treatment of neurotic disorders. Its "tranquilizing" effects appeared to be no better than or different from those of a barbiturate. A number of controlled studies have since appeared, and several of these do show meprobamate to be superior to placebos in the relief of neurotic anxiety and tension. During this same period, however, a number of other controlled studies have shown no difference in effectiveness between meprobamate and placebos in patients with various neurotic disorders, including children with behavior problems.

One of the favorable studies (K. Rickels, et al., JAMA, 171:1649, 1959) found meprobamate to be superior to amobarbital in neurotic outpatients. It is of interest to compare this study with an earlier controlled study (M. J. Raymond, et al., Brit. Med. J., 2:63, July 13, 1957) which found that amobarbital was su-

perior to meprobamate. In both studies, the dosage of meprobamate was 400 mg., four times a day. The total daily dosage of amobarbital was 300 mg. in the Raymond study, but only 120 mg. in the later Rickels study. Despite the use of larger doses of amobarbital by Raymond and his associates, there was no essential difference in the number and kind of side effects between amobarbital and meprobamate. Since even in a double-blind trial, comparisons have little significance unless optimum dosages are used, the results obtained with the low dosage of amobarbital in the Rickels study must be questioned.

In another controlled study (E. H. Uhlenhuth, et al., Am. J. Psychiatry, 115: 905, 1959) 400-mg. doses of meprobamate taken four times a day were found to be superior to a placebo in neurotic outpatients, but no better than 16 mg. of phenobarbital taken four times a day.

CONCLUSIONS - The evidence of various controlled studies on meprobamate is clearly conflicting. Nevertheless, in the totality of studies available in the literature, including both the new data and the data reported in the review by Lateis and Weiss, Medical Letter consultants do not find convincing evidence that meprobamate affords any distinct advantage over appropriate doses of the barbiturates either as a hypnotic or as a daytime sedative for the relief of neurotic anxiety or tension.

Furthermore, as pointed out by J. O. Cole, G. L. Klerman and R. T. Jones (Progress in Neurology and Psychiatry, Vol. 15, 1960, Chapter 33), "There is increasing evidence that meprobamate can produce serious complications, including addiction and withdrawal symptoms, convulsions, coma, psychotic behavior and even death. These complications are often associated with high dosage. Minor withdrawal symptoms, similar to those which can occur with the barbiturates, may occur with meprobamate, in doses over 1200 mg. daily."

While it is true that in the great majority of patients meprobamate in small doses (less than 1200 mg. daily) is a relatively innocuous agent, the severe side effects that are occasionally seen, the risk of addiction with prolonged use, the high price (about 12¢ per 400-mg. tablet), and the lack of convincing evidence that it is safer or more effective than appropriate doses of barbiturates, hardly make meprobamate a drug of choice for relief of neurotic anxiety or tension.

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Sworn to and subscribed before me this 30th day of September, 1960, Max Kalichstein, Notary Public, State of New York

Arthur Kallet, Managing Director

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